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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,617	05/14/2001	Jerome B. Zeldis	9516-022	7262

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EXAMINER
LEWIS, PATRICK T

ART UNIT	PAPER NUMBER
1623	11

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,617	ZELDIS ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *12-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5-6, 10* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-11) in Paper No. 9 dated February 28, 2003 is acknowledged. The traversal is on the ground(s) that a single search directed to thalidomide and a topoisomerase inhibitor would necessarily encompass all of the claims of groups I-V. This is not found persuasive because a search of methods for treating cancer would not necessarily encompass the methods of Groups II-V. Invention I is drawn to a method for treating cancer. Invention II is drawn to method for increasing the dosage of topoisomerase inhibitor that can be safely and effectively administered. Invention III is drawn to method of reducing or preventing an adverse effect associated with chemotherapy. Invention IV is drawn to method of reducing or preventing an adverse effect associated with radiation therapy. Invention V is drawn to a method of increasing the therapeutic efficacy of a topoisomerase inhibitor. The different inventions are drawn to distinct processes with different modes of operation, function, and effects. It would indeed impose an undue burden upon the examiner in charge of this application if the instant restriction requirement were not advanced as set forth herein.

The requirement is still deemed proper and is therefore made FINAL.

2. Claim 12-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction requirement in Paper No. 9 dated February 28, 2003. The restriction requirement is made FINAL herein.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A written description analysis involves three principle factors:

1. Field of the invention and predictability of the art
2. Breadth of the claims
3. For each claimed species/genus, possession of claimed invention at the time of the filing.

The breadth of the claim is such that any primary or metastatic cancer may be treated comprising administering a therapeutically effective amount of any topoisomerase inhibitor, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, and a therapeutically effective amount a thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof. The specification discloses the treatment of metastatic colorectal cancer by administering irinotecan and thalidomide. The support in the specification is not adequate for the

claim to the treatment of any primary or metastatic cancer comprising administering a therapeutically effective amount of any topoisomerase inhibitor, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, and a therapeutically effective amount a thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof.

The written description requirement for a claimed genus may be satisfied through sufficient description of an adequate representation of species by functional characteristics sufficient to show the applicant was in possession of the claimed genus. There are a variety of cancers and compounds which function as topoisomerase inhibitors, each with a certain degree of specificity for which there is not seen adequate support for treatment or use in the instant disclosure. There is limited predictability in the art that any one compound or class of compounds is capable of treating cancer broadly. To provide adequate support for the breadth of the claims, applicant would have to provide sufficient evidence that a population of individuals suffering from a variety of cancers were treated by administering thalidomide and an adequate representation of species of compounds recognized in the art as topoisomerase inhibitors. The data presented shows the treatment of metastatic colorectal cancer by administration of thalidomide and the specific topoisomerase inhibitor irinotecan; however, this does not correlate via art recognized evidence or adequate support in the instant disclosure to the treatment of cancer broadly by administering any topoisomerase inhibitor and thalidomide as broadly claimed. An adequate representation of species requires that the species which are expressly described and

recognized in the art as representative of the entire genus. What constitutes a "representative number" is an inverse function of the predictability in the art in question. As such, a skilled artisan would not recognize that a compound capable of treating colorectal cancer would be representative in function to treatment of cancer broadly. As such, there is not seen any data or correlative prior art evidence which supports applicant's claim that at the time of filing, the application/administration of the compounds of the invention was applied to a population of individuals suffering from cancers broadly with a variety of topoisomerase inhibitors.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 5 and 7-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "SN-38", "GG-211", "DX-8951f", "UCE6", "UCE1022", "TAN-1518A", "TAN-1518B", "KT6006", "KT6528", "ED-110", "NB-506", "ED-110", "NB-506", "Hoescht dye 33342", "Hoechst dye 33258", "BC-4-1", "IST-622", and "XR-5000" have not been defined adequately defined in the specification or claims. In the absence of a chemical name or structure correlative to said terms, all claims reading upon said terms are seen to be indefinite. The examiner suggest in the first occurrence of each alphanumeric compound designation, applicant provide a sufficient identity, i.e. a chemical name or structure.

Claims 8-11 recite a concentration range for irinotecan or SN-38 employed in the treatment method. The amount of irinotecan or SN-38 employed in the treatment method is unclear as applicant merely recites a concentration range. In the absence of the amount of irinotecan or SN-38 employed, said claims are indefinite as one of ordinary skill in the art would not be apprised of the metes and bounds of the dosage regiment intended.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marx et al. Proc. Am. Soc. Clin. Onocology (1999), Vol. 18, page 454a (Marx); Pitot et al. Journal of Clinical Onocology (1997), Vol. 15, pages 2910-2919 (Pitot); and Priel et al. U.S. Patent 5,622,959 (Priel) in combination.

Claim 1 is drawn to a method of treating primary cancer comprising administering a therapeutically effective amount of any topoisomerase inhibitor, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, and a therapeutically effective amount a thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof. Claim 2 is drawn to a method of treating metastatic cancer comprising administering a therapeutically effective amount of any topoisomerase inhibitor, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, and a therapeutically effective amount a thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof. Claims 3-11 ultimately depend from claims 1 or 2. Claim 3-4 places limitations on the type of cancer treated. Claims 5-7 limit the topoisomerase inhibitor employed. Claims 8-11 limits the amount thalidomide used. The ambiguity of the concentration ranges of irinotecan or SN-38

(topoisomerase inhibitors) recited in claims 8-11 makes it impossible for the examiner to accurately determine the dosage of irinotecan or SN-38 employed in the instantly claimed method. Since the dosage of irinotecan or SN-38 has not been recited in said claims, the examiner has interpreted said claims as reading upon a therapeutically effective amount of irinotecan or SN-38 for the treatment of colorectal cancer.

Marx teaches thalidomide as an antiangiogenic agent in the treatment of advanced cancer (1751). The cancers that are treated include brain, melanoma, breast, colon, mesothelioma and renal cell carcinoma. Thalidomide was administered as an oral daily dose of 100 to 500 mg/day.

Marx differs from the instantly claimed invention in that Marx does not teach the co-administration of a topoisomerase inhibitor. However, the deficiencies of Marx would have been obvious to one of ordinary skill in the art at the time of the invention when viewed in combination with the teachings of Pitot and Priel.

Pitot teaches the administration of CPT-11 [irinotecan] for the treatment of metastatic colorectal carcinoma. Pitot teaches that CPT-11 was administered in 500mL of 5% dextrose solution (page 2912, Treatment Administration).

Priel teaches that camptothecin (CPT) has a strong antitumor activity against a wide range of experimental tumors and human colon cancer (column 2, lines 39-45).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine thalidomide and a topoisomerase inhibitor for the treatment of colorectal cancer. As supported by *Ex parte Quadrantil,* 25 USPQ2d 1071 (Bd. Pat. Appl. & Inter. 1992), the use of materials in combination, each of which is known to

function for intended purpose, is *prima facie* obvious. In the absence of some proof of a secondary nature or of some specific limitations which would tip the scale of patentability in the favor of the instantly claimed invention, it would have been obvious to one of ordinary skill in this art at the time of the invention to co-administer two components (thalidomide and a topoisomerase inhibitor), each of which is recognized as having anti-cancer activity as applicant has done with the above cited references before them. Compounds with the functional limitation of topoisomerase inhibition and thalidomide are well recognized in the art for the treatment of cancer individually, and to combine these two classes of compounds to obtain the same result is indeed *prima facie* obvious.

Conclusion

11. Claims 1-60 are pending. Claims 12-60 are withdrawn from further consideration as being drawn to a nonelected invention. Claims 1-11 are rejected. No claim is allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

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May 8, 2003